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Pharmacokinetics of Alendronate

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Abstract

Alendronate (alendronic acid; 4-amino-1-hydroxybutylidene bisphosphonate) has demonstrated effectiveness orally in the treatment and prevention of postmenopausal osteoporosis, corticosteroid-induced osteoporosis and Paget's disease of the bone. Its primary mechanism of action involves the inhibition of osteoclastic bone resorption. The pharmacokinetics and pharmacodynamics of alendronate must be interpreted in the context of its unique properties, which include targeting to the skeleton and incorporation into the skeletal matrix.

Preclinically, alendronate is not metabolised in animals and is cleared from the plasma by uptake into bone and elimination via renal excretion. Although soon after administration the drug distributes widely in the body, this transient state is rapidly followed by a nonsaturable redistribution to skeletal tissues. Oral bioavailability is about 0.9 to 1.8%, and food markedly inhibits oral absorption. Removal of the drug from bone reflects the underlying rate of turnover of the skeleton. Renal clearance appears to involve both glomerular filtration and a specialised secretory pathway.

Clinically, the pharmacokinetics of alendronate have been characterised almost exclusively based on urinary excretion data because of the extremely low concentrations achieved after oral administration. After intravenous administration of radiolabelled alendronate to women, no metabolites of the drug were detectable and urinary excretion was the sole means of elimination. About 40 to

60% of the dose is retained for a long time in the body, presumably in the skeleton, with no evidence of saturation or influence of one intravenous dose on the pharmacokinetics of subsequent doses.

The oral bioavailability of alendronate in the fasted state is about 0.7%, with no significant difference between men and women. Absorption and disposition appear independent of dose. Food substantially reduces the bioavailability of oral alendronate; otherwise, no substantive drug interactions have been identified.

The pharmacokinetic properties of alendronate are evident pharmacodynamically. Alendronate treatment results in an early and dose-dependent inhibition of skeletal resorption, which can be followed clinically with biochemical markers, and which ultimately reaches a plateau and is slowly reversible upon discontinuation of the drug. These findings reflect the uptake of the drug into bone, where it exerts its pharmacological activity, and a time course that results from the long residence time in the skeleton. The net result is that alendronate corrects the underlying imbalance in skeletal turnover characteristic of several disease states. In women with postmenopausal osteoporosis, for example, alendronate treatment results in increases in bone mass and a reduction in fracture incidence, including at the hip.

Alendronate (alendronic acid) is one of a growing class of bisphosphonate compounds in clinical use or under investigation.[1,2] Bisphosphonates are non-hydrolysable analogues of inorganic pyrophosphate in which the bridging oxygen has been replaced by a carbon, with, most commonly, an aliphatic side chain. They were developed after the discovery that pyrophosphate inhibits both the formation and dissolution of calcium phosphate crystals.[3] These properties suggested a potential utility as an inhibitor of bone resorption or ectopic calcification. However, the nearly ubiquitous presence of inorganic pyrophosphatase prevents the direct use of the inorganic compound as a modifier of bone metabolism. In contrast, the bisphosphonates have demonstrated biochemical stability and pharmacological activity as inhibitors of bone resorption and, thus, have an expanding role in the clinical management of patients with bone disease.

Intravenous alendronate has been used investigationally for the management of hypercalcaemia of malignancy.[4-6] Alendronate is approved as an oral medication for both the treatment and prevention of postmenopausal osteoporosis,[7-13] corticosteroid-induced osteoporosis[14] and the treatment of Paget's disease.[15-18] Alendronate is approved for use orally in over 80 countries worldwide.

Alendronate is monosodium 4-amino-1-hydroxybutylidene bisphosphonate (fig. 1). The amino group in the side chain appears to yield much higher potency and far greater selectivity for inhibiting bone resorption, over reducing mineralisation, than is observed with etidronate, one of the first bisphosphonates used clinically and one which does not contain nitrogen.[19]

This review provides some background on the biochemical mechanism of action of bisphosphonates, focusing on studies with alendronate, as it is relevant to a complete understanding of the pharmacokinetics and pharmacodynamics of alendronate and their relationship to each other. Furthermore, because some of the properties of alendronate are characteristic of the bisphosphonate class, notably its limited oral bioavailability and prolonged residence in the target organ of interest (i.e. the skeleton), a brief summary of the preclinical pharmacokinetics of alendronate is provided as several important pharmacokinetic questions with alendronate can only be addressed within animals. Finally, the pharmacokinetic-pharmacodynamic relationship will be reviewed as it relates most importantly to the beneficial effects of alendronate for the treatment of postmenopausal osteoporosis.

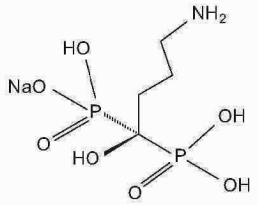

Fig. 1. Structure of alendronate (alendronic acid; monosodium 4-amino-1-hydroxybutylidene bisphosphonate).

1. Mechanism of Action

Although all the details of the pharmacological action of bisphosphonates have not been clearly defined, the data permit a general description of the mechanism of action of alendronate.

Alendronate is rapidly cleared from plasma, either eliminated in the urine or taken up by the skeleton.[20] However, this uptake is not uniform throughout bone; rather, it is focused in areas of high physiological activity, where bone turnover is greatest.[21] Specifically, alendronate concentrates in a relatively selective manner at sites of bone resorption.[21,22]

Following binding to the hydroxyapatite of bone exposed at sites of bone resorption, alendronate can be mobilised by osteoclasts as these cells generate acidic conditions and dissolve the inorganic phase, thereby solubilising the bound alendronate.[23] Alendronate is then taken up by the osteoclasts and, through biochemical effects, renders the osteoclast inactive for bone resorption.[21] This is observable on electron microscopy as a loss of the 'ruffled border' of the osteoclast, a sign that they are no longer active.

Two recently described biochemical effects include an inhibition of protein tyrosine phosphatase[24-26] and inhibition of protein prenylation.[27,28] This latter mechanism appears to result from the inhibition in osteoclasts of enzyme(s) involved in cholesterol biosynthesis by nitrogen-containing bisphosphonates.[27,28] Although numerous other biochemical effects have been described which may lead to the inhibition of osteoclast resorptive capabilities and its structural changes, inhibition of prenylation is most likely the one responsible for yielding a quiescent cell.[2,19] Not only is osteoclast activity reduced, but the number of osteoclasts is also significantly reduced after long term administration of alendronate. Whether this is secondary to the reduction in bone resorption and the dynamics of bone turnover, or a separate effect to reduce osteoclast recruitment and/or differentiation, or induce osteoclast apoptosis,[29] or all of the above, is not certain. Furthermore, some investigators have proposed that bisphosphonates, such as alendronate, must interact with the bone forming cells, the osteoblasts, in order to exert their inhibitory influence on the osteoclasts.[30]

The alendronate deposited at sites of bone turnover, if not taken up by the osteoclasts, is ultimately incorporated within the matrix as newly formed bone encases it.[19,21] This is similar to the tetracyclines, which are deposited in bone along the mineralisation front, a characteristic exploited by investigators who study its fluorescence in bone as a marker of bone formation. The alendronate incorporated in the mineralised bone matrix is no longer pharmacologically active until the time when bone resorption removes the overlaying layers of bone, bringing the alendronate back to the surface and allowing it to interact with osteoclasts again.

Most importantly, these data indicate that the primary effect of alendronate on the skeleton is to inhibit bone resorption. Other manifestations of its skeletal influence after long term administration, such as reduced bone formation and turnover, derive from this primary pharmacological activity.

2. Preclinical Pharmacokinetics

2.1 Metabolism

As with most other bisphosphonates, alendronate appears not to be metabolised in mammals.[31] Following administration of a dose of radiolabelled alendronate, Lin et al.[20] demonstrated, by high performance liquid chromatography (HPLC), that unmodified alendronate accounts for all the radioactivity recovered in urine of rats, dogs and monkeys, as well as that deposited in the skeletons of

rats and dogs, indicating that metabolism of alendronate *in vivo* is absent or at most negligible.

It has recently been reported that other bisphosphonates, for example clodronate, may be metabolised by mammalian cells *in vitro* to yield an analogue of adenosine triphosphate; this could play a role in the mechanism of action of that drug.[32] In contrast, such metabolism was not demonstrable with alendronate.[32]

Because of its high potency, the relatively low oral dosages used clinically produce plasma concentrations of alendronate which fall below the limit of reliable quantification of the assay. The absence of discernible metabolism thus proved essential to examination of the pharmacokinetics of this compound, given that plasma pharmacokinetics after oral administration could not be quantified. Drug uptake was, therefore, characterised by following deposition in bone of radiolabelled drug. For example, bioavailability was examined by determining the ratio of ^{14}C and ^{3}H in bone following administration of a ^{14}C-labelled oral dose and a ^{3}H-labelled intravenous dose.[20]

2.2 Absorption

As with other bisphosphonates, the oral absorption of alendronate in animals is limited under fasting conditions and negligible in the presence of food. The fasting oral bioavailability of alendronate was estimated as 0.9% in rat, 1.8% in dog and 1.7% in monkey.[20] Oral administration to rats in the presence of food decreases bioavailability about 6- to 7-fold.[20] Since alendronate is highly polar and charged at physiological pH, absorption across the gastrointestinal tract has been proposed to occur primarily by the paracellular, rather than transcellular, route.[33] Alendronate is better absorbed from segments of the gastrointestinal tract with larger surface areas, that is the jejunum > duodenum > ileum.[33]

2.3 Distribution

Over the concentration range of 0.1 to 0.5 mg/ml, alendronate is approximately 80, 73 and 70% protein bound in rats, dogs and monkeys, respectively. Albumin is the predominant protein that binds alendronate, with pH and calcium concentra-

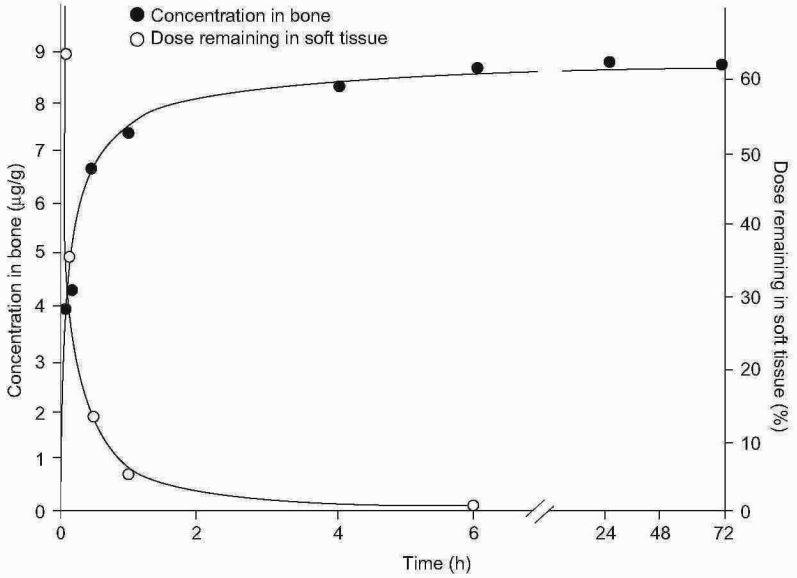

Fig. 2. Distribution of alendronate to soft tissues and bone in rats (n = 3 to 4) following administration of a single intravenous dose of 1 mg/kg.[20]

tion modulating the extent of alendronate binding.[31,34]

An intravenous dose of alendronate 1 mg/kg in rats is quickly and widely distributed throughout the body followed by redistribution to its ultimate site of sequestration (bone) or elimination. About 63% of the dose is present in noncalcified tissues at 5 minutes post-dose. This is reduced to about 5% by 1 hour and about 1% at 6 to 24 hours post-dose. A reciprocal pattern is evident in bone, where about 30% of the dose can be found 5 minutes after administration, reaching some 60 to 70% of dose by 1 hour, and remaining constant for the next 71 hours (fig. 2).[20]

Distribution of alendronate within bone is determined by blood flow and favours deposition at sites of the skeleton undergoing active resorption. Thus a larger proportion of the dose is taken up by trabecular as compared with cortical bone, and in the latter at the metaphysis compared with the diaphysis.[20] The uptake of alendronate in the skeleton was linear (proportional to dose) in rats which received radiolabelled alendronate (0.2, 1 or 5 mg/kg intravenously or 1, 5 or 25 mg/kg orally).[20] When multiple intravenous doses (totalling 35 mg/kg) were given to rats every 3 days for 21 days, the bone deposition of the first (^{3}H-labelled) and last (^{14}C-labelled) doses was similar. Thus, the uptake of drug in bone was not saturated with repeated doses, nor did prior administration of alendronate affect the distribution of subsequent doses, at least up to the extent of drug delivered in this experiment.[35]

2.4 Elimination

Alendronate is cleared from plasma by deposition in bone and urinary excretion. Only a negligible amount of the drug (<0.2%) is detected in faeces after intravenous administration, suggesting little, if any, is excreted in bile. About 30 to 40% of a 1 mg/kg dose in rats is eliminated in the urine by 24 hours post-dose.[20] About 60 to 70% of an alendronate dose is sequestered in bone over the short term. The drug is then slowly released from the skeletal deposits, accounting for the prolonged multiple-phase elimination of this drug.[20] The terminal half-life ($t_{½\gamma}$) of alendronate is related to the rate of bone turnover in each of the species studied; thus a half-life of approximately 300 days in rats and at least 1000 days in dogs has been estimated.[20]

The observation that the renal clearance of alendronate in the rat exceeded that expected from the glomerular filtration rate and unbound concentration of the drug suggested that a secretory mechanism was involved in renal elimination. Renal excretion of alendronate appears to utilise an active secretory system with a maximum rate of about 25 mg/min/kg in the rat.[36] High concentrations of classical inhibitors of the secretion of acidic (probenecid, *p*-aminohippuric acid) and basic (quinine and cimetidine) compounds do not influence urinary excretion of alendronate in the rat.[36] However, etidronate, a structurally related member of the bisphosphonate class, did reduce the renal clearance of alendronate in a dose-dependent manner, as did high concentrations of inorganic phosphate.[36] Dose-dependent decreases in renal function induced in rats by administration of increasing doses of uranyl nitrate produced graded reductions in renal clearance of alendronate with increases in bone deposition.[36]

In summary, the preclinical pharmacokinetics of alendronate are similar to those of other bisphosphonates and permit construction of the model depicted in figure 3. Many of the experiments supporting the model cannot be performed in humans. However, as the data will show, the available information strongly indicate that this model also applies to the pharmacokinetics of alendronate in humans.

3. Clinical Pharmacokinetics

The pharmacokinetics of bisphosphonates in humans have been characterised to a limited extent. These compounds are difficult to measure in biological fluids and their disposition characteristics make it difficult to examine their pharmacokinetic behaviour in plasma. Concentrations in plasma following therapeutic doses generally fall below

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